CASE REPORT

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An Unprecedented Association; Coronary Artery Disease and Sagliker Syndrome

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Abstract

Sagliker syndrome (SS) develops in chronic kidney disease patients because of insufficiently treated secondary hyperparathyroidism (SHPT) at an early stage. Studies indicating the potential association of the pathophysiology of the syndrome with genetic mutations are available. Phenotypic characteristics such as Brown tumors, lytic non-neoplastic bone lesions resulting from abnormal bone metabolism, deformities in the mandible and maxilla, irregularly spaced teeth, hypertrophic prominence of the lips, short neck, and slender upper and lower extremities are prominent in these patients. Brown tumors are often found in the metaphyses of the long bones, pelvis, maxilla, and costae, with significant involvement observed in our patient's bilateral costae. The facial deformities in our patient were consistent and similar to the phenotype findings in other cases reported in the literature. In patients with chronic kidney disease (CKD), anemia is frequently observed because of increased SHPT, with a direct toxic effect on erythropoietin synthesis and erythropoietin progenitors in bone marrow. While anemia is common, bone marrow fibrosis and pancytopenia are much rarer. Although hyperparathyroidism is considered to be the responsible factor in the pathophysiology of SS, the literature does not report an association between SS and bone marrow fibrosis, making our case the first presentation of such an association. The high prevalence and early onset of coronary artery diseases (CAD) in patients with CKD are associated with a combination of systemic inflammation, oxidative stress, hypertension, vascular calcification, and disruptions in bone metabolism. In the patient's medical history, there was no presence of hypertension, diabetes, smoking, or a family history of these conditions. SHPT in end-stage renal disease has been shown to accelerate vascular calcification and subclinical atherosclerosis. The presence of early-onset CAD in our patient, despite the absence of traditional risk factors, raises the question of whether hyperparathyroidism, a prominent factor in this syndrome, played a significant role in its etiology.

Keywords: Renal osteodystrophy, secondary parathyroidism, hypercalcemia, brown tumor, angina, coronary angiography

INTRODUCTION

Sagliker syndrome (SS) is a rare condition in which secondary hyperparathyroidism (SHPT) and chronic renal failure (CKD) co-exist. First described in 2004, this syndrome is typically seen in young women (18-39 years), and its association with CKD is very rare (0.05%).[1,2] While the pathophysiologic factor responsible for SS has been shown to be hyperparathyroidism secondary to CKD, *GNAS1* gene mutation has been demonstrated in 40% of SS patients.[3] Although renal transplantation may halt the progression of musculoskeletal deformities, it may not reverse SS-related deformities.[4] Patients frequently present with deformities of the upper and lower jaw, dental abnormalities, marked lip hypertrophy, short neck, short stature, bone deformities, deformities of the hands and fingertips, and psychiatric disorders. Although patients with CKD are at high risk for coronary artery disease (CAD), cases of bone marrow myelofibrosis secondary to hyperparathyroidism in CKD have been reported in the literature, but no case of co-existence of SS, CAD, and bone marrow fibrosis has been reported. In this case

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report, we present the case of a patient with SS who continued to exhibit persistent deformities in long-term follow-up despite undergoing two parathyroidectomies, with the comorbidity of existing CAD and severe pancytopenia.

CASE REPORT

A 39-year-old woman presented to the outpatient clinic with exertional dyspnea, joint pain, and leg weakness. She had been on hemodialysis for 5 years because of end-stage renal failure. Her medical history revealed that she underwent kidney transplantation in 2012 and had a history of rejection 2.5 years after transplantation. Two years earlier, coronary imaging of the patient showed 80-90% stenosis after lymphadenectomy D2, 30-40% stenosis after CX OM1, and 20-30% stenosis in the middle segment of the right coronary artery with anterior origin. She had undergone 2.75x16 mm Promus Premier (Boston Scientific) stent implantation for a critical lesion in the left anterior descending artery (Figure 1, 2). There was also no known history of diabetes, family history, or smoking. Physical examination revealed a dialysis fistula in the right arm (Figure 3), dental deformities, malocclusion, caries, protruding lips, enlargement of the mandible and maxilla, short neck, short stature (Figure 4), finger deformities (Figure 5), and weakened lower extremities, with distinct phenotypic features consistent with SS, which is rare in patients with CKD compared with cases in the literature. Blood pressure and pulse rate were within the normal range. Cardiac auscultation revealed a 2/6 diastolic murmur in the mesocardia focus, and abdominal palpation revealed splenomegaly. In the medical history of the patient, it was reported that parathyroidectomy was performed 8 years ago and weakness, fatigue, and serum parathyroid hormone level was 1,989 ug/L three years after the operation. The patient underwent a second parathyroidectomy. However, despite two parathyroidectomies, the deformities persisted in the long-term follow-up. At the last nephrology clinic evaluation, fluorodeoxyglucose (FDG) positron emission tomography-computed tomography was ordered because of diffuse bone pain and revealed a 44 mm enlarging sclerotic lesion in the right 9th rib (An Unprecedented Association; CAD and SS ure 6), a similar lesion with 37 mm FDG uptake in the left 10th rib, a 1 cm lytic lesion in the right femoral neck, and a l (Figure 6, 7). Brown tumors were reported on tru-cut biopsy of lytic bone lesions. Simultaneous parathyroid evaluation revealed minimal FDG uptake in a paratracheal location, and

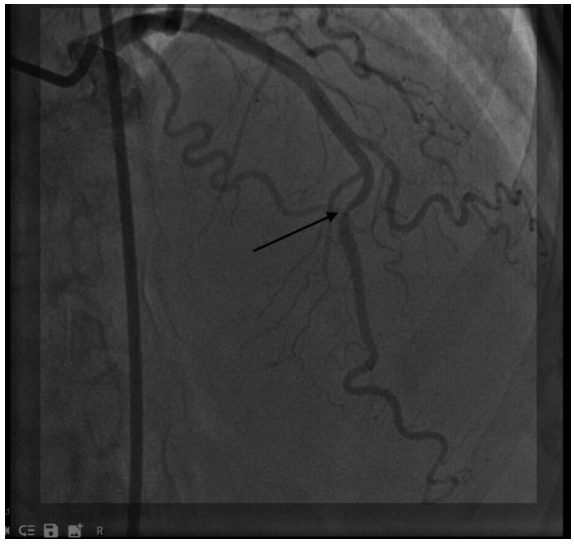

Figure 1. Coronary angiography revealed 80-90% stenosis in the left anterior descending coronary artery (lymphadenectomy)

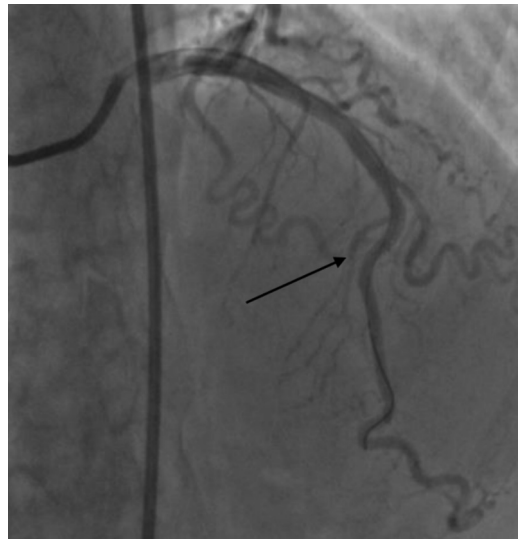

Figure 2. After lymphadenectomy D2, a 2.75x16 16 mm Promus stent was implanted

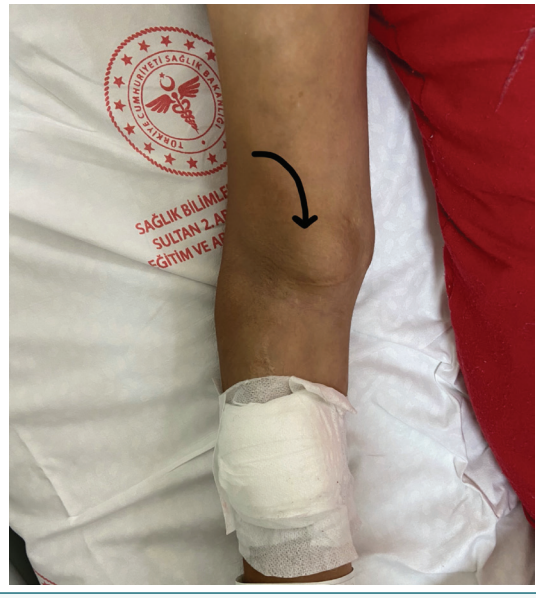

Figure 3. Dialysis fistula was observed in the patient's arm

methoxy-isobutylisonitrile (MIBI) scintigraphy revealed focal increased MIBI uptake in the upper level of the left thyroid lobe. In the last laboratory findings in our clinic, parathyroid level was 277 ng/L, alkaline phosphatase level was 116 U/L, Ca level was 8.18 mg/dL and p=2.07 mg/dL. Although CAD remained stable, the patient's white blood cell count was 1.69 mm^3, hemoglobin was 8.8 g/dL, hematocrit was 19.8, and platelet count was 61 mm^3. Hematologic evaluation was requested but the patient refused. The patients history revealed two bone marrow biopsies resulting in myelofibrosis. Medical treatment included cinacalcet, acetylsalicylic acid 100 mg, clopidogrel 75 mg, bisoprolol 12.5 mg, atorvastatin 40 mg, pantoprazole 40 mg, sevelamer carbonate, trimethazidine 80 mg, doxazosin 8 mg xl, folic acid, nifedipine 30 mg. Transthoracic echocardiography revealed an ejection fraction of 60%, moderate aortic valve regurgitation, mild to moderate tricuspid valve regurgitation, calcified mitral and aortic valves with adequate patency, and pulmonary artery pressure of 45 mmHg. The patient did not have a detected mutation associated with the *GNAS1* gene (Table 1). Informed consent of the patient was obtained.

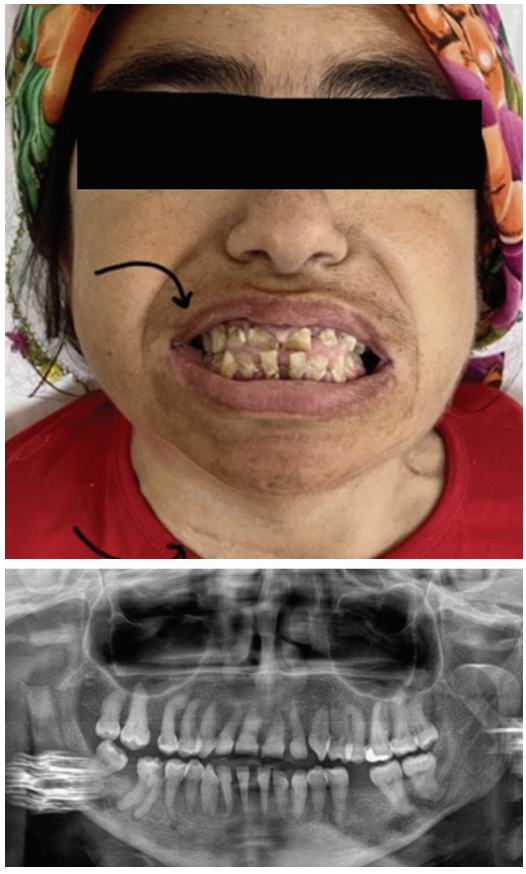

Figure 4. The patient exhibits dental deformities, gaps, decay, protruding lips, and widening of the mandible and maxilla, along with a short neck

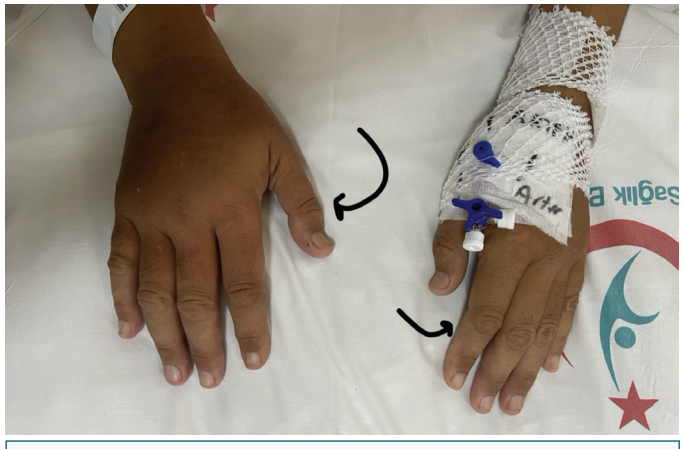

Figure 5. The patients fingers show deformities

DISCUSSION

SS is a syndrome that develops because of inadequately treated SHPT in the early stages of chronic kidney disease (CKD). Studies also suggest an association between the pathophysiology of SS and genetic mutations. Missense mutations in exons 1, 4, 5, 7,10 and 13 of the *GNAS1* gene are the most common mutations associated with SS. In addition, cytogenetic chromosomal abnormalities and calcium-sensing receptor mutations have been described.[5] Abnormal bone metabolism in these patients leads to lytic non-neoplastic bone lesions known as brown tumors, deformities of the mandible and maxilla, irregularly spaced teeth, hypertrophic lips, short stature, and thin upper and lower extremities, all of which present as distinct phenotypic features. Brown tumors frequently occur in the metaphysis of the long bones, pelvis, maxillae, and ribs; in our patient, they were prominently present in the bilateral ribs. The facial deformity observed in our patient is compatible with the phenotypic findings of other cases reported in the literature.[6]

Anemia in patients with CKD frequently occurs due to increased SHPT and leads to direct toxic effects on erythropoietin synthesis and erythropoietin progenitors in the bone marrow. However, bone marrow fibrosis and pancytopenia are much rarer conditions.[7] Although hyperparathyroidism is accepted as a responsible factor in the pathophysiology of SS, the association between SS and bone marrow fibrosis has not been reported in the literature, which makes our case the first

Table 1. Biochemical parameters

Parathyroid	277 ng/L
Alkaline phosphatase	116 U/L
Calsiyum	8.18 mg/dL
Phosphor	2.07 mg/dL
Hemoglobin	8.8 g/dL
Hematocrit	19.8
Platelet	61 mm^3
White blood cell	1.69 mm^3

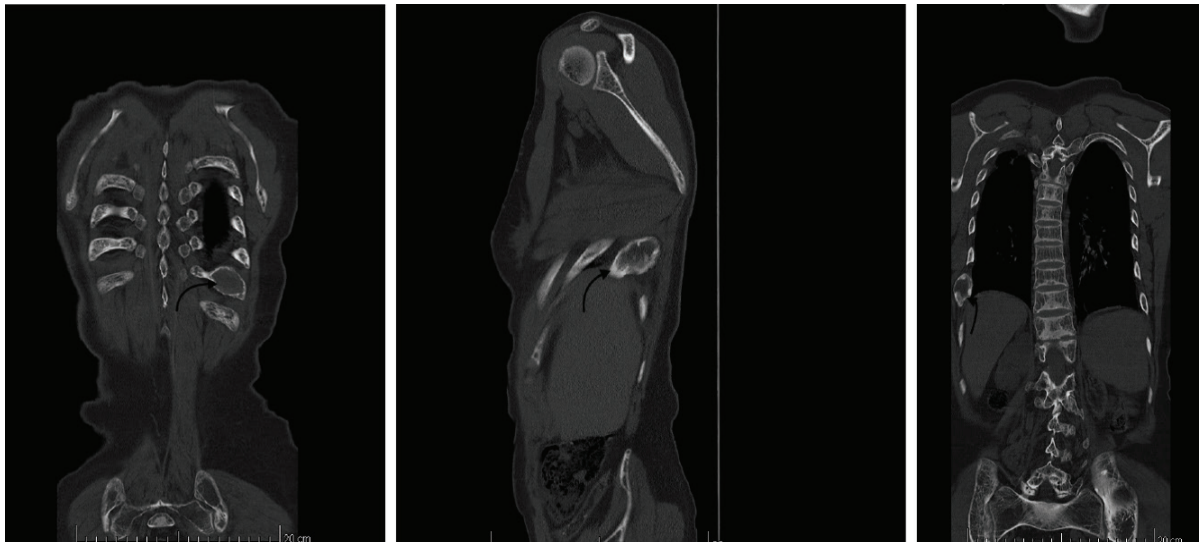

Figure 6. CT scan of the patient reveals an expansive sclerotic lesion with a width of 44 mm and a thickness of 20 mm at the posterolateral aspect of the right 9th rib

CT: Computed tomography

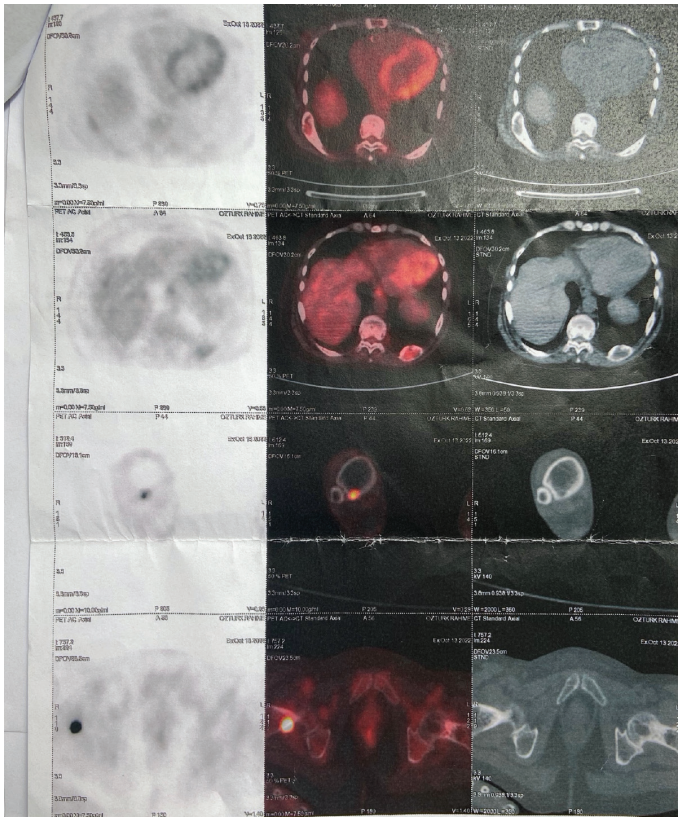

Figure 7. The patient was found to have a lesion in the intramedullary area with mild FDG uptake, and based on the trucut biopsy of lytic bone lesions, the lesions present in the left 10th and right 9th ribs appear to be consistent with brown tumors

FDG: Fluorodeoxyglucose

report of such an association. The high prevalence and early onset of CAD in patients with CKD have been associated with a combination of systemic inflammation, oxidative stress, hypertension, vascular calcification, and disturbances in bone metabolism.[6]

Our patient did not have risk factors such as hypertension, diabetes, smoking, or a positive family history of anemia. In patients with end-stage renal disease, SHPT accelerates vascular calcification and subclinical atherosclerosis in addition to renal osteodystrophy.[8] Although our patient did not have traditional risk factors, the onset of CAD at an early age raises the question of whether hyperparathyroidism, which is an important factor in the etiology of this syndrome, is the primary contributing factor. Our patient's coronary lesion was non-calcific lesion. The reason why the lesion does not appear calcific in our patient coronary angiography may be that the patient is a premenopausal female patient at a relatively young age. It has been stated that vascular inflammation may be less in women than in male patients in CKD patients[9], but if we had the opportunity to evaluate the coronary lesion under intravascular ultrasound images, we could clarify the characteristic findings of the lesion. SHPT can lead to abnormal functions of various organs, such as ectopic calcification of blood vessels and tissues and pathological fractures, which increase the disability rate and the incidence of cardiovascular events.[10] The main treatment of SS involves lowering serum phosphorus levels; therefore, treatment modalities such as the use of phosphorous binders and dialysis may be used. Vitamin D and calcium replacement or parathyroid surgery may be used.[10]

CONCLUSION

SS is a rare complication observed in patients with CKD. Our patient contributed to the literature with his clinical history, extensive systemic involvement, and genetic analysis of SS. In particular, in young patients with CKD, the risk of SS, CAD, and bone marrow fibrosis due to hyperparathyroidism may increase. It is crucial to raise awareness for the regular control and follow-up of such cases. Increased vigilance and awareness can significantly impact prognosis, leading to early diagnosis and appropriate treatment options.

Ethics

Informed Consent: Informed consent of the patient was obtained.

Authorship Contributions

Surgical and Medical Practices: N.E.D., M.U., Concept: İ.Y., N.E.D., M.U., Design: İ.Y., Data Collection or Processing: İ.Y., Analysis or Interpretation: İ.Y., N.E.D., M.U., Literature Search: İ.Y., N.E.D., M.U., Writing: İ.Y., N.E.D., M.U.

Conflict of Interest: No conflict of interest was declared by the authors.

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